REMARKS

Claims 1-26 are currently pending. Claims 3-9 and 12-18 are withdrawn from further consideration and are canceled herein without prejudice. Claims 1-2, 10-11, 19-26 are amended herein to clarify the claimed subject matter. New claims 27-32 are submitted herewith. Accordingly, instant claims 1-2, 10-11, and 19-32 are under consideration.

Support for amendment to the claims is found throughout the specification and in the original claims. Specifically, support for amendment to claims 1, 19, and 23 is found in original claims 1, 19, and 23 and, for example, in Figure 1 and at page 5, lines 8-28 (lines 14-15 in particular); and at page 19, lines 18-19, wherein support for covalent attachment of the 5' end of the hairpin nucleic acid to the 3' end of the single-stranded template nucleic acid to produce a hairpin-template complex having a covalently attached 5' overhang is found. Support for amendment to claims 2, 11, 20, 22, 24, and 26 is found in original claims 2, 11, 20, 22, 24, and 26 and, for example, at page 20, lines 6-7. Support for amendment to claims 10, 21, and 25 is found in original claims 10, 21, and 25 and, for example, at page 6, line 12 through to page 7, line 3 (lines 18-20 in particular); at page 14, lines 14-25; and at page 19, lines 18-19, wherein support for covalent attachment of the 5' end of the double stranded anchor nucleic acid to the 3' end of the single-stranded template nucleic acid to produce an anchor-template complex having a covalently attached 5' overhang is found. No issue of new matter is introduced by these amendments.

Support for new claims 27-32 is found throughout the specification and in the original claims. Specifically, support for new claim 27 is found in original claim 11 and, for example, at page 7, lines 5-16. Support for new claim 28 is found in original claim 11 and, for example, at page 7, lines 5-16; and at page 20, lines 5-7 and lines 24-27; and at page 31, lines 8-10. Support for new claims 29 and 30 is found, for example, at page 22, line 29 through to page 23, line 3. Support for new claim 31 is found, for example, at page 22, line 29 through to page 23, line 9; at page 6, line 12 through to page 7, line 3 (lines 18-20 in particular); at page 14, lines 14-25; and at page 19, lines 18-19. Support for new claim 32 is found, for example, at page 22, line 29

through to page 23, line 3; at page 20, lines 5-7 and lines 24-27; and at page 31, lines 8-10. No issue of new matter is introduced by these amendments.

Rejection under 35 USC § 112

Claims 1-2, 10-11, and 19-26 have been rejected under 35 U.S.C. § 112, second paragraph, for allegedly indefiniteness for recitation of the phrase "the complementary nucleic acid strand" in claims 1 and 10. Claims 1 and 10 are amended herein to clarify the claimed subject matter. In view of amendments to claims 1 and 10, the rejection, as it applied to claims 1-2, 10-11, and 19-26, is respectfully traversed.

In view of the amendments to the claims, the Examiner is respectfully requested to reconsider the validity of the rejection of the claims under 35 U.S.C. §112 and withdraw the rejection.

Rejections under 35 USC § 103

Claims 1, 10, 19, 21, 23, and 25 are rejected under 35 USC § 103(a) as allegedly unpatentable over Nazarenko et al. [United States Patent Number (USPN) 6,090,552; issued 2000) in view of Cheeseman et al. (USPN 5,302,509; issued 1994) and in further view of Gonzalgo et al. (USPN 7,037,650; filed June 2001). In view of the clarifying amendments to the claims and Applicant's arguments, this rejection is respectfully traversed.

To begin, Nazarenko et al. do not teach step (a)(ii) of the instant claims. The hairpin-template complex of the present invention comprises a hairpin nucleic acid and a single-stranded template nucleic acid, wherein the 5' end of the hairpin nucleic acid is covalently attached to the 3' end of the single-stranded template nucleic acid and attachment of the single-stranded template nucleic acid generates a hairpin-template complex comprising a 5' overhang. With regard to claims directed to anchor-template complexes having a covalently attached 5' overhang, the Nazarenko et al. reference is also defective because it fails to present guidance relating to an anchor-template complex comprising a double-stranded anchor and a single stranded template nucleic acid, wherein the 5' end of the first end of the double-stranded nucleic

acid anchor is covalently attached to the 3' end of the single-stranded template nucleic acid. The Examiner refers Applicant to Figure 1 of Nazarenko et al. with respect to the hairpin primer of this reference. It is noteworthy that the hairpin primer shown in Figure 1 binds to the target nucleic acid via **hybridization** to the single stranded region extending from the 3' end of the hairpin primer. See, for example, Figure 2 of Nazarenko et al. It is apparent that this interaction does not involve the 5' end of the hairpin primer or the 3' end of the template. Indeed, as shown in Figure 2, the 5' end of the hairpin primer is **not** attached to the single stranded target nucleic acid as claimed in the instant method, nor is the 3' end of the template attached to the hairpin primer. Each respective termini is "unattached". This point also applies with respect to the anchor-template complex. Although the term "attached" with respect to the template and hairpin primer is defined in the present specification as meaning that the template nucleic acid is covalently attached to the hairpin (see page 19, lines 18-19), the present claims are amended herein to explicitly recite this aspect of the invention. That being the case, it should, therefore, be apparent that the 3' end of the single stranded target nucleic acid of Nazarenko et al. is not covalently attached to the 5' end of the hairpin primer as claimed in the present invention. This structural difference is further reflected in the presence of a covalently attached 5' overhang in the hairpin-template complex of the present invention, which is conferred by attachment of the 3' end of the single stranded target nucleic acid to the 5' end of the hairpin primer. The absence of a covalently attached 5' overhang in the hairpin-template complex of Nazarenko et al. is evidenced by the structure of such complexes as depicted in Figures 2 and 3, for example. The anchor-template complexes of the present invention are also structurally distinct in this regard.

In addition to the above structural distinction, Nazarenko et al. also fails to motivate an ordinarily skilled artisan to arrive at the present invention in several other respects. Applicant concurs with the Examiner that Nazarenko et al. do not teach a method wherein the sequence of the nucleic acid template is determined by addition of dNTPs to the 3' end of the hairpin which acts a primer. The Examiner relies on Cheeseman et al. for teaching directed to sequence determination. Applicant asserts, however, that there is no teaching or guidance in Nazarenko et al. that would lead an ordinarily skilled practitioner to combine the method taught therein with

steps directed to sequence determination. As described therein, the Nazarenko et al. patent relates to oligonucleotides for amplification of nucleic acids that are detectably labeled with molecular energy transfer (MET) labels. More specifically, it relates to a method for detecting amplification products generated using these oligonucleotides. The method of Nazarenko et al. is designed to permit detection of amplification products without prior separation of unincorporated oligonucleotides and allows detection of the amplification product directly, by incorporating the labeled oligonucleotide into the product. It is notable that Nazarenko et al. do not teach a sequencing step in any of the methods described therein and clearly, therefore, do not teach a second sequencing step. In that the instant method calls for a sequencing step [step (b)(i)] and a second sequencing step [step (e)] that follows treatment with sodium bisulfite [step (d)], Nazarenko et al. fail to teach at least these three recited method steps. In view of the above directive of Nazarenko et al., namely to detect amplification products, and in the absence of any teaching relating to sequencing of the nucleic acid template, Applicant asserts that there is no motivation to combine the teachings of Nazarenko et al. and Cheeseman et al.

Applicant further agrees with the Examiner's assessment that Nazarenko et al. do not teach a method wherein after the elongated strand is nicked and strand displacement occurs, the template strand is then treated with sodium bisulfite and resequenced. The Examiner also recognizes that Nazarenko et al. do not teach comparing the initial sequence determination with the second resequencing determination to detect the presence of methylated cytosine in the template. The Examiner relies on Gonzalgo et al. for teaching relating to the ability of sodium bisulfite to convert unmethylated cytosine residues to uracil residues while leaving 5-methyl cytosines unchanged. Applicant asserts, however, that there is no teaching or guidance in Nazarenko et al. that would inspire one of skill in the art to consider a determination of cytosine methylation status in the template nucleic acid as useful in the context of generating detectable amplification products. As detailed throughout USPN 6,090,552 and recapitulated above, the method of Nazarenko et al. is directed to the generation of detectably labeled amplification products. Accordingly, Nazarenko et al. fail to offer any guidance pertaining to stepwise sequencing of individual nucleotides in a template and, within this same context, also fail to

provide any reason to evaluate cytosine methylation status in a template.

In that these references fail collectively to teach the hairpin-template complex of the present invention, wherein the 3' end of the single stranded target nucleic acid is attached to the 5' end of the hairpin primer to generate a 5' overhang and the use of such a molecular entity in subsequent recited steps of the claimed method, these references are defective with respect to several recited features of the present invention. These references are equally defective with respect to an anchor-template complex of the invention and their use in the recited steps of the claimed method. Thus, the profound defects of the primary reference, namely Nazarenko et al., are not remedied by the teachings of Cheeseman et al. and/or Gonzalgo et al. Moreover, there is no motivation presented in these references that would lead a skilled practitioner to combine the disparate methods taught therein to arrive at the present invention. The ultimate objective of Nazarenko et al. is to generate detectable amplification products from nucleic acid templates; it is simply not directed to an analysis of the templates on the level of sequencing by synthesis or resequencing to assess cytosine methylation status. That being the case, the deficiencies of the Nazarenko et al. patent are not remedied by the teachings of Cheeseman et al. and/or Gonzalgo et al. Accordingly, these references, alone and in combination, fail to render obvious the instantly claimed method. In view of the above, Applicant respectfully requests reconsideration of the rejection of claims 1, 10, 19, 21, 23, and 25 under 35 USC § 103(a) and withdrawal of this rejection.

Claims 2, 11, 20, 22, 2, and 26 are rejected under 35 USC § 103(a) as allegedly unpatentable over Nazarenko et al. [United States Patent Number (USPN) 6,090,552; issued 2000) in view of Cheeseman et al. (USPN 5,302,509; issued 1994) and in further view of Gonzalgo et al. (USPN 7,037,650; filed June 2001) and in further view of Chernov et al. (US 2004/0086866; filed October 2002). Applicant has interpreted the Examiner's rejection as applicable to claims 2, 11, 20, 22, **24**, and 26, rather than to claims 2, 11, 20, 22, **2**, and 26 as indicated in the Office Action. Clarification in this regard is respectfully requested. In view of the clarifying amendments to the claims and Applicant's arguments, this rejection is respectfully traversed for the reasons set forth herein below.

The defects of Nazarenko et al. when considered alone or combination with Cheeseman et al. and/or Gonzalgo et al. are outlined above and are incorporated herein in their entirety. The Examiner acknowledges and Applicant concurs that the combined references do not teach that the hairpin probes are attached to a solid substrate. The application of Chernov et al. describes methods and compositions for creating double-stranded nucleic acid (e.g. dsDNA) microarrays. The Examiner relies on Chernov et al. for teaching the use of hairpin probes attached to a microarray. The Chernov et al. application fails to remedy any of the substantial defects outlined above with respect to the combined teachings of Nazarenko et al., Cheeseman et al., and Gonzalgo et al. Applicant, therefore, asserts that these references in combination fail to render obvious the instantly claimed method. In view of the above, Applicant respectfully requests reconsideration of the rejection of claims 2, 11, 20, 22, 24, and 26 under 35 USC § 103(a) and withdrawal of this rejection.

In view of the above, the Examiner is deferentially requested to reconsider and withdraw the rejection of the claims under 35 U.S.C. §103.

Provisional Rejection Under the Judicially Created Doctrine of Obviousness-Type Double Patenting

The Examiner has provisionally rejected claims 1-2, 10-11, and 19-26 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 4-5 and 17-18 of co-pending application 10/537,188. A Terminal Disclaimer is attached hereto, the filing of which is believed to overcome the above rejection of pending claims 1-2, 10-11, and 19-26 of the present invention under the judicially created doctrine of obviousness-type double patenting.

Fees

No fees are believed to be necessitated by this amendment. However, should this be an error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment or to credit any overpayment.

Conclusion

It is submitted, therefore, that the claims are in condition for allowance. No new matter has been introduced. Allowance of all claims at an early date is solicited. In the event that there are any questions concerning this amendment, or application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,

Veronica Mallon

Veronica Mallon, PhD.
Agent for Applicant(s)
Registration No. 52,491

KLAUBER & JACKSON
411 Hackensack Avenue
Hackensack, New Jersey 07601
(201) 487-5800

March 28, 2007

Enclosures: Terminal Disclaimer
Information Disclosure Statement